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Original Article

Design and evaluation of Matrix Transdermal therapeutic system of Repaglinide

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ABSTRACT: The present study is an attempt to develop a Matrix type transdermal system capable of delivering the selected antidiabetic drug Repaglinide in the desired therapeutic concentration for prolong period. The principle of transdermal drug delivery systems is to deliver drug across epidermis to achieve systemic effect over a prolonged period of time. Because of these attributes, transdermal drug delivery systems offer many advantages such as reduced side effects, improved patient compliance, elimination of first-pass metabolism, and sustained drug delivery. Anti-diabetic drug which is important for the treatment of hyperglycemic disorders. This category of anti-diabetic drugs is rapid and almost completely absorbed from the GIT following oral administration, but undergoes extensive first pass metabolism. Therefore, the peak plasma concentration occurs rapidly and after a single oral dose and bioavailability is 56%, the half-life of elimination is 1 hour in normal subject. Hence, it is required to design a drug delivery system which may deliver anti- diabetic drug Repaglinide in controlled manner for a prolonged period to circumvent the drug related side effects. Considering all these problems associated with oral administration of anti-diabetic drug Repaglinide, attempt has been made to develop transdermal drug delivery system in order to achieve a better release pattern.

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INTRODUCTION

Transdermal is a viable administration route for potent, low molecular weight therapeutic agents which cannot withstand the hostile environment of the gastrointestinal tract and/or are subject to considerable first-pass metabolism by the liver.Globally, the occurrence of diabetes is increasing at an alarming rate. Type-II diabetes represents about 98% of all diabetes cases, in population older than 45 years of age.

Medication-related problems leading to morbidity and mortality are quite common with the disease. For diabetic patients, medication becomes an integral part of life and noncompliance of therapy may lead to chronic complications. Management strategies need to tackle public-health issues such as obesity and lack of exercise as well as incorporating drugs that address the underlying pathophysiology of type-II diabetes.

Fortunately, our understanding of that pathophysiology is now becoming clearer and this knowledge is to yield new agents of therapeutic promise such as Repaglinide.

Repaglinide is a short-acting oral hypoglycemic agent used as a prandial glucose regulator in the management of type -II diabetes mellitus. The drug possesses low oral bioavailability (56 %) due to hepatic first pass metabolism after oral administration and poor absorption in the upper intestinal tract. It has a very short biological half-life of ~1h, which makes frequent dosing necessary to maintain the drug within the therapeutic blood level for longer period.

Moreover, it produces hypoglycemia; causes gastrointestinal adverse effects including abdominal pain, diarrhoea, constipation, nausea and vomiting after oral administration. Because diabetes is a chronic disease hence the treatment is intended over a prolonged period.

Transdermal delivery systems may provide a useful drug therapy about patient compliance. Transdermal delivery can bypass the first pass metabolism and deliver the drug in a rate-controlled manner, which is desirable in anti-diabetic therapy. With this view, an attempt will be made to deliver Repaglinide in effective therapeutic concentration in TDDS form[1-5].

MATERIALS & METHODS

Materials

Repaglinide was obtained as a gift sample from Alkem Laboratories, Mumbai. Eudragit RS 100, Eudragit RL100 & HPMC from Evonik Degussa India pvt.Ltd.,Mumbai. Double Distilled water was used throughout the study & all other chemicals and solvents were analytical reagent grade and purchased from commercial suppliers.

Methods

Preparation of Transdermal patches[6-8]

The transdermal patches were prepared by solvent evaporation method. Different polymers (Eudragit RS 100, Eudragit RL 100 and HPMC) alone and in combination were accurately weighed and dissolved in 20 ml solvent. Known volume of Dibutyl pthalate was used as plasticizer and oleic acid used as permission enhancer and mixed thoroughly with help of magnetic stirrer. 90 mg of drug was dissolved in the solution and mixed for 10mins. The resulted uniform solution was poured into petri-dish and kept for the evaporation after 24hrs a dried film were out and stored in desiccators.

Table 1: Preparation of Matrix Transdermal Patches

Ingredients	FORMULATIONS						
	F1	F2	F3	F4	F5	F6	F7
Repaglinide (mg)	15	15	15	15	15	15	15
HPMC(mg)	130	260	-	-	-	-	-
Eudragit RL 100(mg)	-	-	130	260	-	-	130
Eudragit RS 100(mg)	-	-	-	-	130	260	130
Oleic acid(ml)	0.20ml	0.20ml	0.20ml	0.20ml	0.20ml	0.20ml	0.20ml
Dichloro methane(ml)	10	10	20	20	20	20	20
Ethanol(ml)	10	10	-	-	-	-	-
DibutylPthalate(%)	15%	15%	15%	15%	15%	15%	15%

Evaluation of Transdermal patches

The prepared Repaglinide transdermal patches were evaluated as mentioned below.

1. **Physical appearance**[9-11]:All the transdermal systems were visually inspected for colour, clarity, flexibilityand smoothness.
2. **Folding Endurance**[9-12]:The folding endurance was measured manually for the prepared films. A strip of film (4×3cm) was cut evenly and repeatedly folded at the same place till it broke.Thenumber of times the film could be folded at the same place without breaking gave thefolding endurance value.
3. **Thickness of the films**[13-15]:The thicknesses of the films were measured using Digital Screw Gauge micrometer(Mitutoyo, Japan) at three different places.
4. **Weight uniformity**[10-13]:The dried patches were weighed on electronic balance (Satorius UK). The averageof 3 observations was calculated and S.D values calculated.
5. **Surface pH**[11-15]:For the determination of surface pH three patches of each formulation were allowed to swell for 2 hrs in a petri dish containing 5 ml of phosphate buffer pH 7.4. The surface pH was measured by pH paper placed on the surface of patches and allowed to equilibrate for 1 min. The average of the three readings was recorded.
6. **Drug content**[9-14]:Four piece of 1 cm2 each (1cm × 1cm) were cut from different parts of the film. Each was taken in separate conical flaskscontaining 100ml of suitable dissolutionmedium (MIPB pH 7.4) stirred vigorously for 6h using magneticstirrer.The abovesolutions were filtered and suitable dilutions were made. Absorbance was recorded using UV visible spectrophotometer at their respective wavelengthagainst a blank solution which was prepared by following the same procedure containing the patch without drug.
7. **Percentage moisture uptake**[7-9]:The weighed films were kept in a desiccator at room temperature for 24hrs. It wasthen taken out and exposed to 84% relative humidity using a saturated solution ofpotassium chloride in desiccator until constant weight achieved. The films wereweighed and percent moisture uptake was calculated by using the following formula:

$$\%\text{Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

8. **Percentage moisture content**[7-10]:The prepared films were weighed individually and kept in a desiccator containingfused calcium chloride at room temperature for 24hrs. The films were weighed and percent moisture content was calculated using the following formula:

$$\%\text{ Moisture content} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

9. ***In-vitro* drug release studies**[7-12]:

a) ***In-vitro* Drug Release:** The fabricated film was placed on the semi permeable membrane and attached to the modified diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±10°C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UV spectrophotometer at 236 nm.

b) **Kinetics of drug release:** To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q0-Q) v/s t], Higuchi's square root of time (Q v/s √t) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t.

10. **Accelerated stability studies for the optimized formulation**[10-13]:Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life." Studies designed to increase the rate of chemical degradation or physical change of an active drug substance or drug product by using exaggerated storage conditions as a part of the formal, definitive, storage programme.The optimized formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The optimized formulation was sealed in an aluminum foil and stored at 30±2ºC, 65±5% RH and at 40±2ºC, 75±5% RH for 2 months. Patches were periodically removed and evaluated.

RESULT

Evaluation of Transdermal patches

1. **Weight of the patch** The Weight of Transdermal patches of F1 to F7 varies from 137.4 mg to 271.5 mg and is given in the Table 2.
2. **Thickness of the patch** Thickness of Transdermal patches varies from 0.14 to 0.22mm of F1 to F7 is shown in Table 3.
3. **Moisture uptake:** Moisture uptake of Transdermal patches varies from 4.16 %to 10.18 % of F1 to F7 is shown in Table 4
4. **Moisture content:** Moisture content of Transdermal patches varies from 3.61 % to 5.31 % of F1 to F7 is shown in Table 5.
5. **pH:** pH of Transdermal patches varies from 6.44 to 7.11 of F1 to F7 is shown in Table 6.
6. **Folding Endurance** Folding Endurance of Transdermal patches varied from 205.2 to 216.1 of F1 to F7 and is shown in Table 7.
7. **Drug content determination** Drug content of Transdermal patches, F1 to F7 varies between 93.1 % to 98.4 % and is shown in Table 8.
8. ***In vitro* drug release studies:** The maximum cumulative % drug release for formulation F1 to F7 are shown in the Tables 9 to 15.*In vitro* release profiles are shown in figures 1-4. The data obtained was fitted to zero order, first order, and Higuchi's square root of time and Korsemeyer-Peppas equations to understand the mechanism of drug release from the Repaglinide Transdermal patches. The co-efficient determination indicated that the release data was best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism.
9. **Stability Studies** Physiochemical evaluation of F6 during Stability Studies of F6 during Stability Studies are shown in the Table 17.

Table 2: Weight Variation

S.No.	Formulation	Weight Variation (mg)(Mean ± SD)
1	F1	142.2±1.321
2	F2	271.5±0.512
3	F3	140.3±0.623
4	F4	268.7±1.59
5	F5	137.4±1.12
6	F6	263.2±0.76
7	F7	267.8±0.84

*All values are expressed as mean ± SD (n = 3)

Table 3: Thickness

S.No.	Formulation No.	Thickness (mm) (Mean ± SD)
1	F1	0.15±0.004
2	F2	0.18±0.01
3	F3	0.14±0.003
4	F4	0.19±0.01
5	F5	0.14±0.006
6	F6	0.22±0.004
7	F7	0.21±0.001

*All values are expressed as mean ± SD (n = 3)

Table 4:Moisture uptake

S.No.	Formulation No.	Moisture uptake (%)(Mean ± SD)
1	F1	7.25 ±0.26
2	F2	10.18 ±0.41
3	F3	5.12±0.34
4	F4	6.21±0.51
5	F5	4.16±0.46
6	F6	4.83±0.55
7	F7	4.94±0.61

*All values are expressed as mean ± SD (n = 3)

Table5: Moisture content

S.No.	Formulation	Moisture content (%)(Mean ± SD)
1	F1	4.48 ±0.38
2	F2	5.31±0.32
3	F3	4.24±0.43
4	F4	4.51±0.53
5	F5	3.44±0.52
6	F6	3.61±0.65
7	F7	3.81±0.41

*All values are expressed as mean ± SD (n = 3)

Table7: Folding Endurance

S.No.	Formulation	Folding Endurance (Mean ± SD)
1	F1	211.5 ±1.51
2	F2	205.2±1.54
3	F3	215.1±1.45
4	F4	208.7±1.64
5	F5	210.3±1.53
6	F6	216.1±1.41
7	F7	212.2±1.49

*All values are expressed as mean ± SD (n = 3)

Table 6: pH

S.No.	Formulation	pH(Mean ± SD)
1	F1	6.44 ±0.52
2	F2	6.91±0.55
3	F3	6.88±0.41
4	F4	7.11±0.57
5	F5	6.94±0.51
6	F6	7.15±0.61
7	F7	6.88±0.45

*All values are expressed as mean ± SD (n = 3)

Table 8: Drug Content

S.No.	Formulation	Drug Content (%) (Mean ± SD)
1	F1	95.5 ±0.21
2	F2	93.1±0.24
3	F3	96.4±0.41
4	F4	97.2±0.34
5	F5	97.1±0.44
6	F6	98.2±0.25
7	F7	98.4±0.29

*All values are expressed as mean ± SD (n = 3)

Table 9: *In vitro* drug release study of Formulation F1

S.No.	Time (Hrs)	√T	Log T	Cumulative % of drugreleased	LogCumulative % drugreleased	Cumulative% of drugremained	LogCumulative % drugremained
1	0.5	0.707107	-0.30103	12.31	1.090258	87.69	1.94295
2	1	1	0	25.56	1.407561	74.44	1.871806
3	2	1.414214	0.30103	35.45	1.549616	64.55	1.809896
4	4	2	0.60206	45.56	1.658584	54.44	1.735918
5	6	2.44949	0.778151	55.58	1.744919	44.42	1.647579
6	8	2.828427	0.90309	62.56	1.796297	37.44	1.573336
7	10	3.162278	1	68.15	1.833466	31.85	1.503109
8	12	3.464102	1.079181	72.15	1.858236	27.85	1.444825

Table 10:*In vitro* drug release study of formulation F2

S.No.	Time (Hrs)	√T	Log T	Cumulative% of drugreleased	LogCumulative% drugreleased	Cumulative% of drugremained	LogCumulative% drugremained
1	0.5	0.707107	-0.30103	11.31	1.053463	88.69	1.947875
2	1	1	0	22.56	1.353339	77.44	1.888965
3	2	1.414214	0.30103	31.15	1.493458	68.85	1.837904
4	4	2	0.60206	40.56	1.608098	59.44	1.774079
5	6	2.44949	0.778151	50.45	1.702861	49.55	1.695044
6	8	2.828427	0.90309	58.89	1.770042	41.11	1.613947
7	10	3.162278	1	65.58	1.816771	34.42	1.536811
8	12	3.464102	1.079181	68.78	1.837462	31.22	1.494433

Table 11:*In vitro* drug release study of formulation F3

S.No.	Time (Hrs)	√T	Log T	Cumulative% of drugreleased	LogCumulative% drugreleased	Cumulative% of drugremained	LogCumulative% drugremained
1	0.5	0.707107	-0.30103	9.56	0.980458	90.44	1.956361
2	1	1	0	19.98	1.300595	80.02	1.903199
3	2	1.414214	0.30103	28.87	1.460447	71.13	1.852053
4	4	2	0.60206	38.78	1.588608	61.22	1.786893
5	6	2.44949	0.778151	42.56	1.629002	57.44	1.759214
6	8	2.828427	0.90309	50.56	1.703807	49.44	1.694078
7	10	3.162278	1	54.47	1.736157	45.53	1.658298
8	12	3.464102	1.079181	61.45	1.788522	38.55	1.586024

Table 12:*In vitro* drug release study of formulation F4

S.No.	Time (Hrs)	√T	Log T	Cumulative% of drugreleased	LogCumulative% drugreleased	Cumulative% of drugremained	LogCumulative % drugremained
1	0.5	0.707107	-0.30103	8.78	0.943495	91.22	1.96009
2	1	1	0	18.78	1.273696	81.22	1.909663
3	2	1.414214	0.30103	25.45	1.405688	74.55	1.872448
4	4	2	0.60206	35.45	1.549616	64.55	1.809896
5	6	2.44949	0.778151	42.45	1.627878	57.55	1.760045
6	8	2.828427	0.90309	48.78	1.688242	51.22	1.70944
7	10	3.162278	1	52.45	1.719745	47.55	1.677151
8	12	3.464102	1.079181	59.25	1.772688	40.75	1.610128

Table 13:*In vitro* drug release study of formulation F5

S.No.	Time (Hrs)	√T	Log T	Cumulative% of drugreleased	LogCumulative % drugreleased	Cumulative% of drugremained	LogCumulative%drugremained
1	0.5	0.707107	-0.30103	8.12	0.909556	91.88	1.963221
2	1	1	0	18.45	1.265996	81.55	1.911424
3	2	1.414214	0.30103	24.45	1.388279	75.55	1.878234
4	4	2	0.60206	34.45	1.537189	65.55	1.816573
5	6	2.44949	0.778151	40.58	1.608312	59.42	1.773933
6	8	2.828427	0.90309	45.85	1.661339	54.15	1.733598
7	10	3.162278	1	50.45	1.702861	49.55	1.695044
8	12	3.464102	1.079181	57.78	1.761778	42.22	1.625518

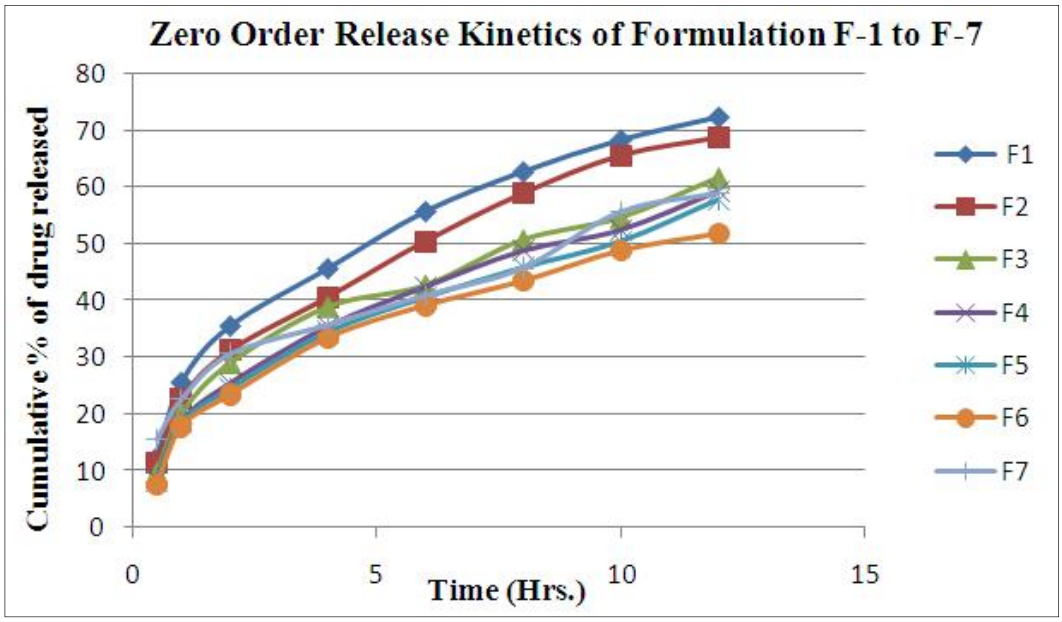
Table 14:*In vitro* drug release study of formulation F6

S.No.	Time (Hrs)	√T	Log T	Cumulative% of drugreleased	LogCumulative% drugreleased	Cumulative% of drugremained	LogCumulative % drugremained
1	0.5	0.707107	-0.30103	7.58	0.879669	92.42	1.965766
2	1	1	0	17.79	1.250176	82.21	1.914925
3	2	1.414214	0.30103	23.45	1.370143	76.55	1.883945
4	4	2	0.60206	33.45	1.524396	66.55	1.823148
5	6	2.44949	0.778151	39.14	1.592621	60.86	1.784332
6	8	2.828427	0.90309	43.45	1.63799	56.55	1.752433
7	10	3.162278	1	48.78	1.688242	51.22	1.70944
8	12	3.464102	1.079181	51.78	1.714162	48.22	1.683227

Table15:*In vitro* drug release study of formulation F7

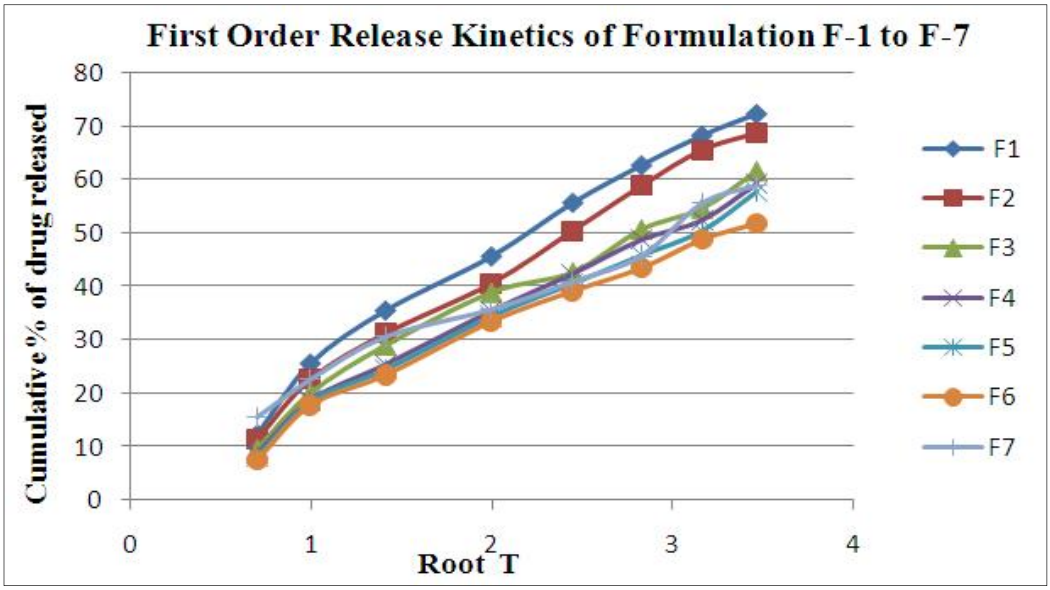
S.No.	Time (Hrs)	√T	Log T	Cumulative % of drugreleased	LogCumulative % drugreleased	Cumulative% of drug remained	LogCumulative% drugremained
1	0.5	0.707107	-0.30103	15.45	1.188928	84.55	1.927114
2	1	1	0	22.45	1.351216	77.55	1.889582
3	2	1.414214	0.30103	30.45	1.483587	69.55	1.842297
4	4	2	0.60206	35.58	1.551206	64.42	1.809021
5	6	2.44949	0.778151	40.78	1.610447	59.22	1.772468
6	8	2.828427	0.90309	45.58	1.658774	54.42	1.735759
7	10	3.162278	1	55.45	1.743902	44.55	1.648848
8	12	3.464102	1.079181	58.78	1.76923	41.22	1.615108

Zero order release Kinetics



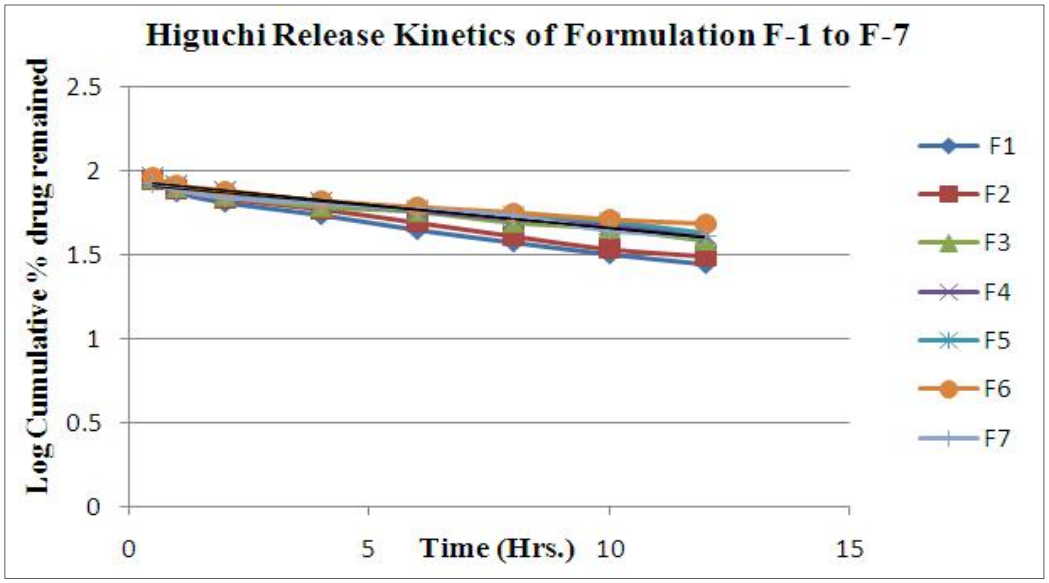
Graph 1: Zero order release Kinetics

First order release kinetics



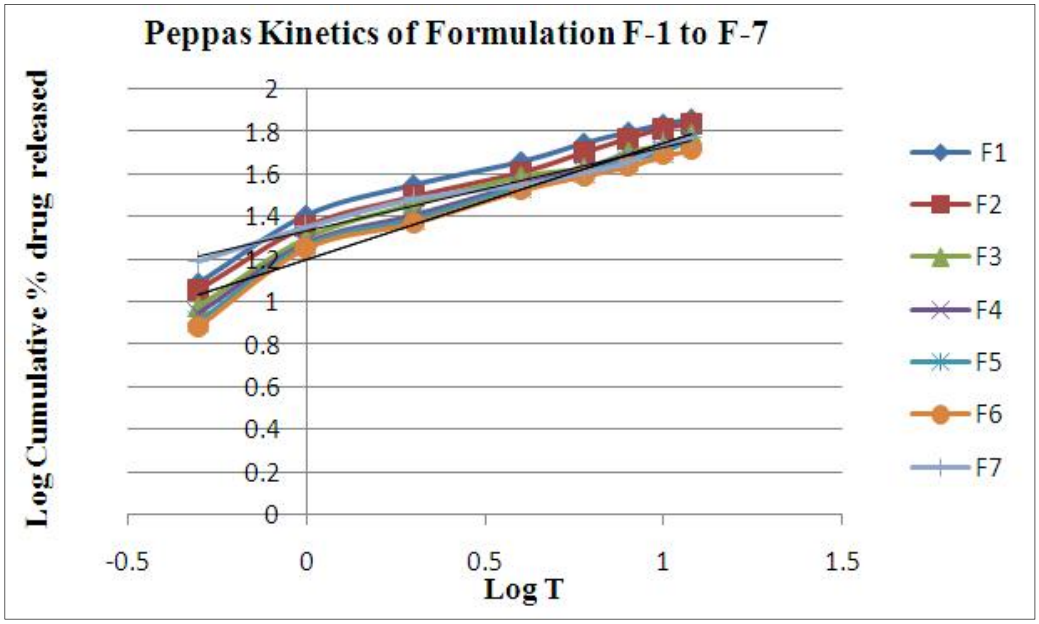
Graph 2: First order release kinetics

Higuchi release kinetics



Graph 3: Higuchi release kinetics

Peppas kinetics



Graph 4: Peppas kinetics

Table 16: Regression co-efficient (R^2) values of Repaglinide transdermal patches according to different kinetic models

Formulation	Regression co-efficient (R^2)				n values for Peppas
	Zero order	First order	Higuchi	Peppas	
F1	0.918	0.981	0.953	0.979	0.66
F2	0.944	0.987	0.943	0.982	0.58
F3	0.927	0.971	0.949	0.968	0.81
F4	0.940	0.975	0.964	0.971	0.62
F5	0.941	0.942	0.956	0.930	0.59
F6	0.918	0.960	0.955	0.945	0.64
F7	0.960	0.977	0.969	0.971	0.72

Stability studies:

Table 17: Physicochemical evaluation of formulation F6 during stability studies

Parameters	0 Days	30 Days		60 Days	
		A	B	C	D
WeightUniformity(mg)	263.2±0.76	263.1±0.56	262.5±0.45	262.9±0.62	262.2±0.71
Patchthickness(mm)	0.22±0.004	0.22±0.006	0.21±0.02	0.21±0.005	0.21±0.05
Foldingendurance	216.1±1.41	214.2±1.51	209.4±1.35	211.3±1.21	205.4±1.11
% MoistureContent	3.61±0.65	3.60±0.35	3.59±0.13	3.58±0.65	3.55±0.48
% Moistureuptake	4.83±0.55	4.81±0.82	4.80±0.34	4.79±0.81	4.74±0.75
% Drugcontent	98.2±0.25	98.17±0.27	98.09±0.38	98.12±0.16	98.02±0.12

***All values are expressed as mean ± SD (n = 3); A, C: 30 ± 2°C/ 65 ± 5% RH; B, D: 40 ± 2°C/ 75 ± 5% RH**

DISCUSSION

Method was developed for the estimation of Repaglinide and showed maximum absorption at wavelength 288 nm in MIPB pH 7.4. The standard calibration curve obeyed Beer's law at the given concentration range of 5µg/ml to 25µg/ml. To investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies were carried out. IR spectrum for pure drug and physical mixture of drug-polymers were obtained and characterized. It was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

Transdermal patches of Repaglinide were prepared by using polymers, like HPMC, Eudragit RL100 and Eudragit RS100. The patches were transparent, smooth and flexible. The results of weight variation, thickness, moisture content, moisture uptake, Folding Endurance, drug content was calculated. The patches F1 to F7exhibited uniform weight ranging from 137.4 mg to 271.4 mg and thickness of F1 to F7 are ranging from 0.14 to 0.22mm. Among the various batches, the uniformity weight and thickness indicates that the polymeric solution of the drug is well dispersed in the patches. All the formulations (F1 to F7) exhibited fairly uniform drug content ranging from 93.1% to 98.4% respectively.

The moisture uptake and Moisture content was found to be low in formulation F3, F4, F5, F6 and F7. This is because of hydrophobic nature of Eudragit polymer compared to HPMC. Folding Endurance of the developed formulations F1 to F7 varied from 205.2 to 243.6. The highest folding endurance was noted for formulation F6.The *in vitro* permeation studies of patches using cellophane membrane barrier was carried out using modified diffusion cell.

The cumulative percentage of drug permeated from F1 to F7 formulations was given in the following order F1 > F2 > F3 > F7> F4 > F5> F6. From the graph, it is evident that drug release is decreased with the increase in concentration of polymer. Eudragit RS 100 and Eudragit RL100 patches have also shown decreased drug release when compared to HPMC patches. The release kinetics was evaluated by making use of Zero order, First order, Higuchi's diffusion and Korsemeyer – Peppa's equation. The drug release through the transdermal patches of Repaglinide follows First order kinetics with diffusion controlled mechanism.

By fitting in the Korsemeyer –Peppas equation the release kinetics follows non-Fickian kinetics. The range of 'n' value for Korsemeyer - Peppas equation -1 to 1. If the 'n' values of Korsemeyer – Peppas equation is below 0.5, which indicates Fickian kinetics. If the 'n' value of Korsemeyer – Peppas equation is in between 0.5 to 1, this indicates non-Fickian kinetics. Here the patches of Repaglinide release kinetics fitted in Korsemeyer – Peppas equation. 'n' values are in between 0.5 to 1, so the release is following non- Fickian, diffusion controlled kinetics. The stability studies were carried out on the most satisfactory formulations F6 at 30 ± 2°C/ 65 ± 5% RH and 40 ± 2°C/ 75 ± 5% RH for two months to assess their long-term stability as per ICH guidelines. At fixed time intervals of 30 days and 60 days, the formulation was evaluated for the physicochemical properties. There was no significant difference in the physicochemical Parameters and were found to be super impossible with the initial readings at zero day results.

CONCLUSION

The preformulation studies involving description, solubility, melting point, of the drug were found to be comparable with the standard. Based on the all the above preformulation studies the drug was suitable for making the transdermal formulation. Based on all these factors the transdermal drug delivery system F1 is having greater % drug release. Formulation F6 having less drug release capacity than other formulations. The formulation F6 shows better extended release up to 12 hrs when compared to other formulations. So, it was concluded that the formulation F6 prepared by using Eudragit RS 100(1:2 ratio)is the better formulation for control release of drug up to 12 hrs of time.

However, the *in vitro* drug release of the best formulation F6 follows first order kinetics and the mechanism of diffusion. Results of the present study encouraged that the Repaglinide with Eudragit RS 100 transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

The stability studies were carried out on the most satisfactory formulations F6 at 30 ± 2°C/ 65 ± 5% RH and 40 ± 2°C/ 75 ± 5% RH for two months to assess their long-term stability as per ICH guidelines. At fixed time intervals of 30 days and 60 days,

the formulation was evaluated for the physicochemical properties, *in vitro* drug release.

There was no significant difference in the physicochemical parameters, *in vitro* drug release profiles were found to be super impossible with the initial readings at zero day results. From the above studies, it is clearly indicated that the Repaglinide transdermal patches containing Eudragit RS 100 in the ratio of 1:2 (F6) was the best formulation among the prepared patches.

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